

The National Cancer Institute's Patient-Derived Models Repository (PDMR)

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Leidos Biomedical Research, Inc. In Support of the Division of Cancer Treatment and Diagnosis, NCI

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<https://pdmr.cancer.gov>

Disclosure Information

AACR Annual Meeting 2018

Yvonne A. Evrard, PhD

I have the following financial relationships to disclose:

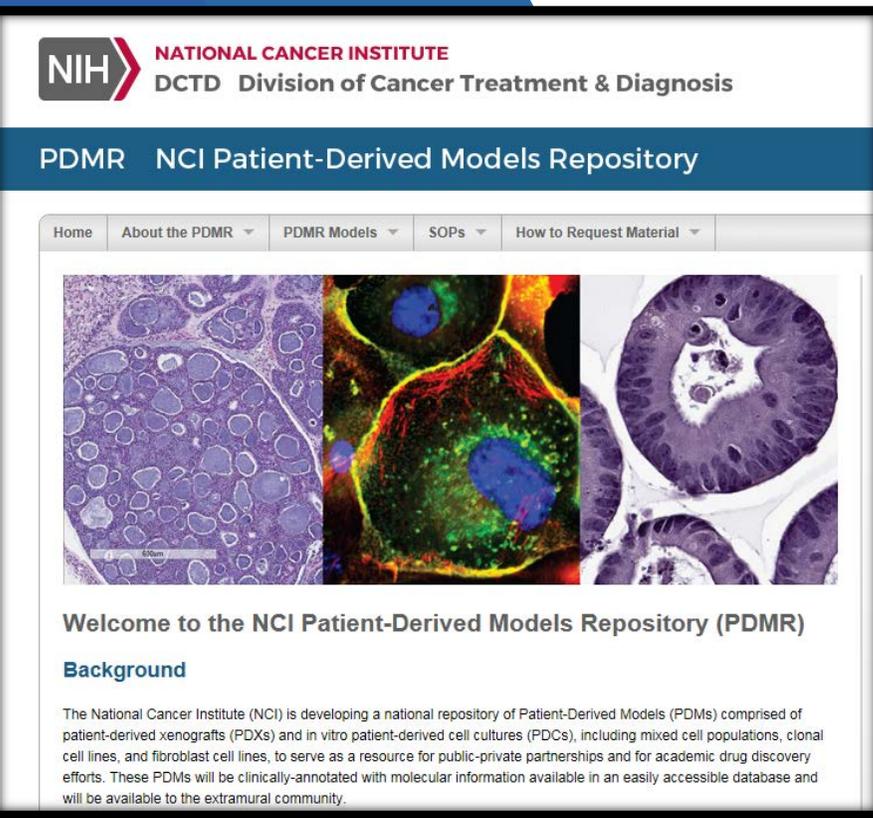
Employee of: Leidos Biomedical Research, Inc.

I will not discuss off label use and/or investigational use in my presentation.

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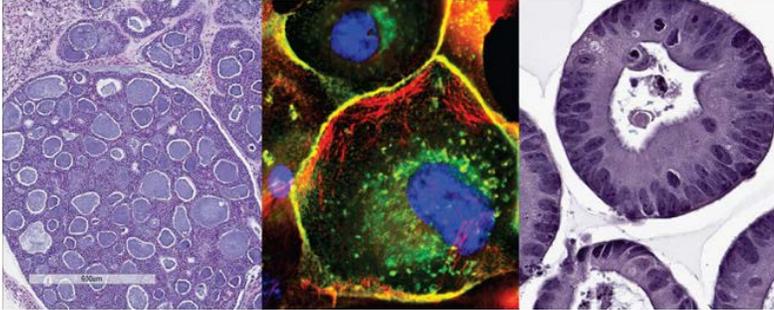
**NATIONAL
CANCER
INSTITUTE**



NIH NATIONAL CANCER INSTITUTE
DCTD Division of Cancer Treatment & Diagnosis

PDMR NCI Patient-Derived Models Repository

Home About the PDMR PDMR Models SOPs How to Request Material



Welcome to the NCI Patient-Derived Models Repository (PDMR)

Background

The National Cancer Institute (NCI) is developing a national repository of Patient-Derived Models (PDMs) comprised of patient-derived xenografts (PDXs) and in vitro patient-derived cell cultures (PDCs), including mixed cell populations, clonal cell lines, and fibroblast cell lines, to serve as a resource for public-private partnerships and for academic drug discovery efforts. These PDMs will be clinically-annotated with molecular information available in an easily accessible database and will be available to the extramural community.

NCI's Patient-Derived Models Repository (PDMR)

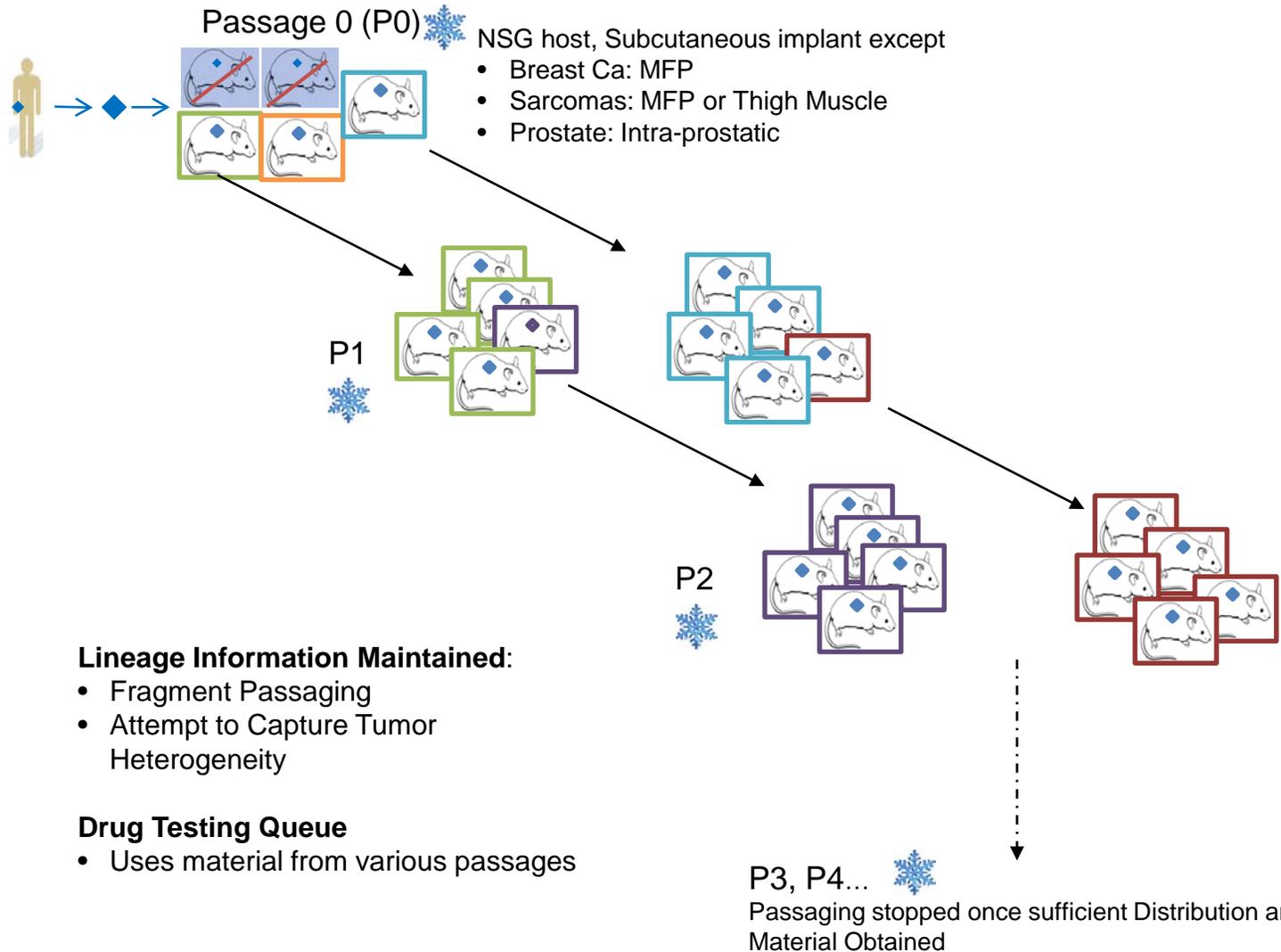
<https://pdmr.cancer.gov>

- Distribute Early-Passage, Clinically-Annotated, and Molecularly-Characterized Patient-Derived Models at a minimal cost to researchers.
- Provide all related metadata and SOPs through a public website.

NCI Patient-Derived Models Repository (PDMR)

- A national repository of Patient-Derived Models (PDMs) to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery comprised of:
 - Clinically-annotated, Early-passage, Molecularly-characterized Patient-Derived Xenografts (PDXs)
 - Complement existing PDX collections and focus on under-represented model types such as rare cancers and models representing racial and ethnic minorities
 - Patient-derived tumor cell (PDCs) and cancer-associated fibroblast (CAF) cultures developed from tumor material and/or PDXs
 - Patient-derived organoid (PDOrg) models developed from tumor material and/or PDXs
- Goal is to provide long-term home for >1000 PDX models along with matched in vitro and organoid models wherever possible
 - Comprehensive characterization of early-passage models: patient medical information including treatment history and response, WES, RNAseq, histology, growth curves, and preclinical drug responses
 - All models and associated data made available through a publicly available website: <https://pdmr.cancer.gov>

PDMR Development and QC Process



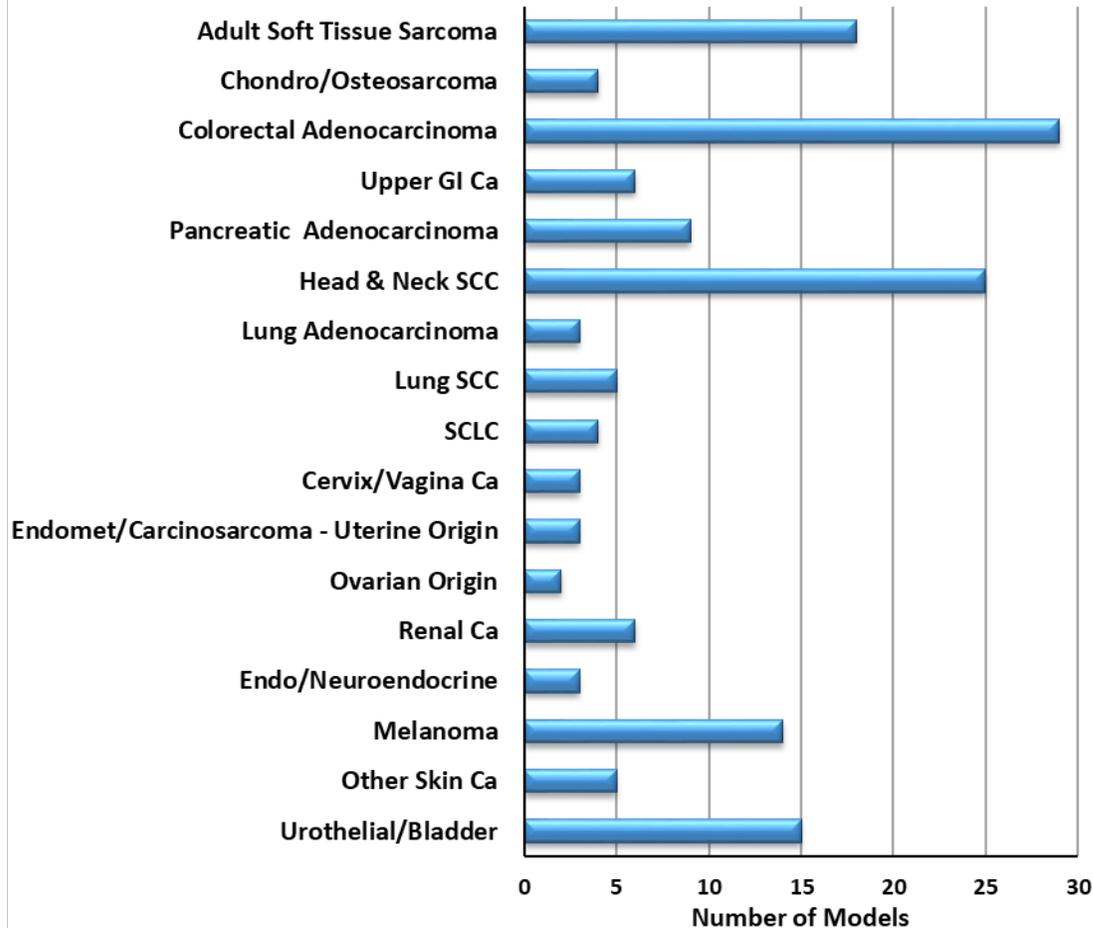
QC General

- Pathology assessed to compare to patient diagnosis and to monitor for EBV-driven human lymphomas, mouse tumors, mouse lymphomas, GvHD...
 - Necropsy of any suspect GvHD, human lymphoma, or metastatic models with indication of disseminated disease
- Confirmation of ability to regrow from Cryopreservation
- Human:Murine DNA Ratio
- Human pathogen testing (hIMPACT panel, IDEXX)
- Rodent pathogen assessment

Distribution Material

- Confirmed for every PDX
 - Pathology
 - STR
- Provided for 4-6 representative PDXs
 - H&E images with %tumor, %necrosis, and %stroma
 - WES and RNASeq

NCI Patient-Derived Models Repository (PDMR)



- Currently have **154 PDX models available** for request (cryo-material) through the public website (pdmr.cancer.gov).
 - Model information also available through PDX Finder at www.pdxfinder.org
- Every model has:
 - Patient medical history including treatment history and response
 - Representative PDX histology images
 - STR Profile
 - Human Pathogen Status
 - WES (FASTQ, vcf) and RNASeq (FASTQ, TPM) from 4-6 representative PDXs
 - Genetic ancestry assessment
- All data are publicly accessible and available for download for metadata analysis and model selection
- Specimens are from patients with both primary and metastatic disease from treatment naïve to heavily pre-treated.

Recently Released & Upcoming Models

New Model Includes Rare Cancers

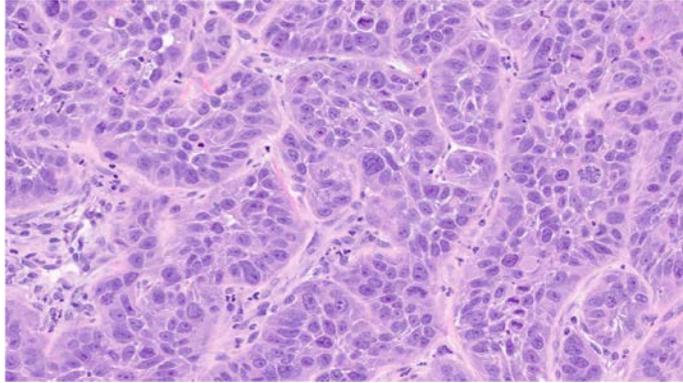
Diagnosis	Currently Available	3-6mo Availability
SCLC	4	0
Merkel Cell Ca	3	0
Small cell ca (extrapulmonary)	2	0
Carcinosarcoma of the uterus	2	3
Hurthle cell neoplasm (thyroid)	1	0
GIST	1	1
Pharyngeal SCC	8	1
Ovarian Epithelial Ca	2	2
Cervical/Vaginal Ca	3	2
Vulvar Ca	1	0
<i>MPNST</i>	<i>0</i>	<i>4</i>
<i>Nasopharyngeal SCC</i>	<i>0</i>	<i>1</i>
<i>Salivary Gland Ca</i>	<i>0</i>	<i>4</i>
<i>Mesothelioma</i>	<i>0</i>	<i>2</i>

Available MSI-High Models

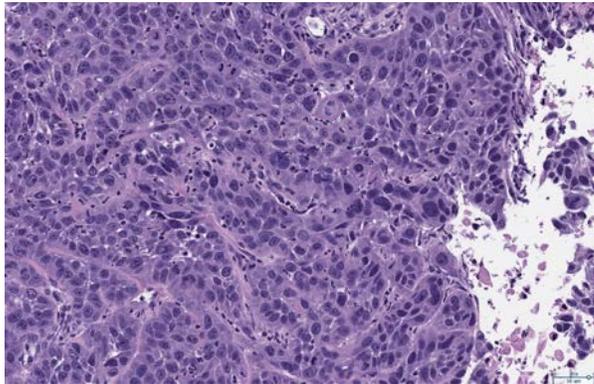
Diagnosis	PDMR Model#
Adenocarcinoma - cervix	235635-245-T
Adenocarcinoma - colon	625472-104-R
Adenocarcinoma - colon	817829-284-R
Adenocarcinoma - colon	997537-175-T
Adenocarcinoma - pancreas	292921-168-R
Carcinosarcoma of the uterus	327498-153-R
Endometrioid endomet. Adeno	381249-077-R
Small cell lung cancer	541946-237-B
Urothelial/bladder cancer, NOS	558786-286-R
Vaginal cancer, NOS	283339-068-R

Tumor Heterogeneity by Histomorphology in One Model

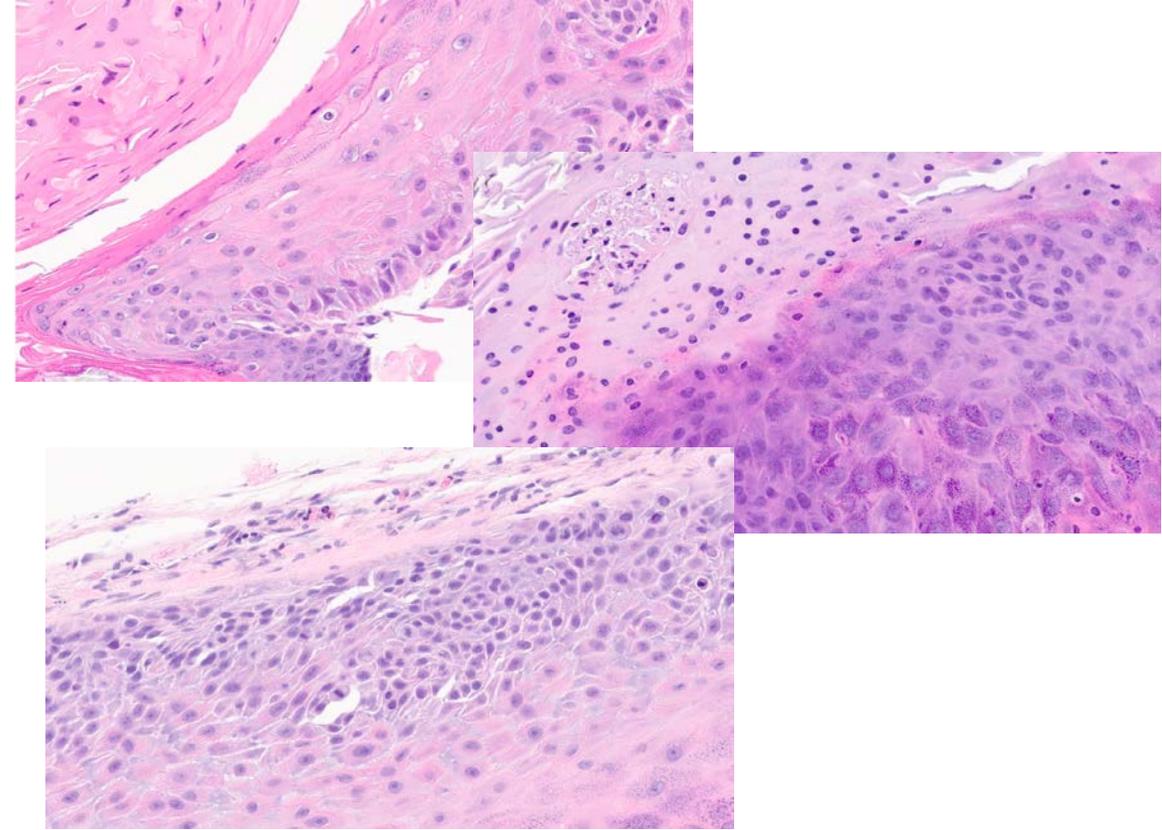
Laryngeal SCC Patient. Resection of the larynx. Tissue implanted into 5 P0 host NSG mice. **Model In development**



P0: Well to moderately differentiated non-keratinizing squamous cell carcinoma.



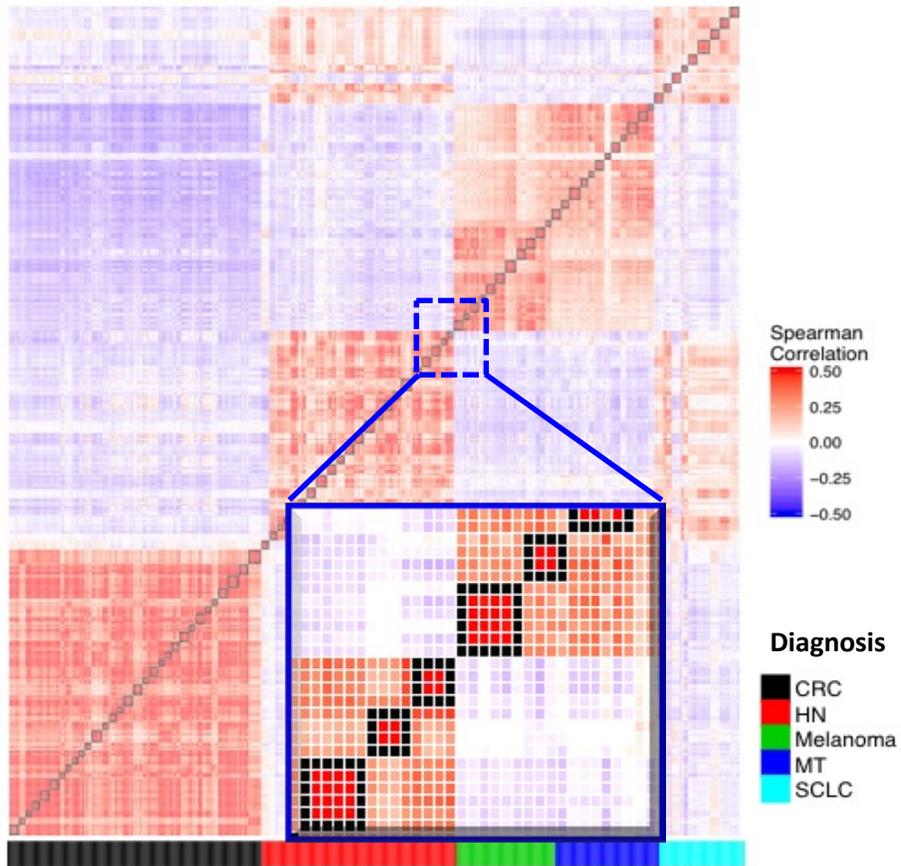
P0: Poorly differentiated squamous cell carcinoma with marked pleomorphism including neuroendocrine features



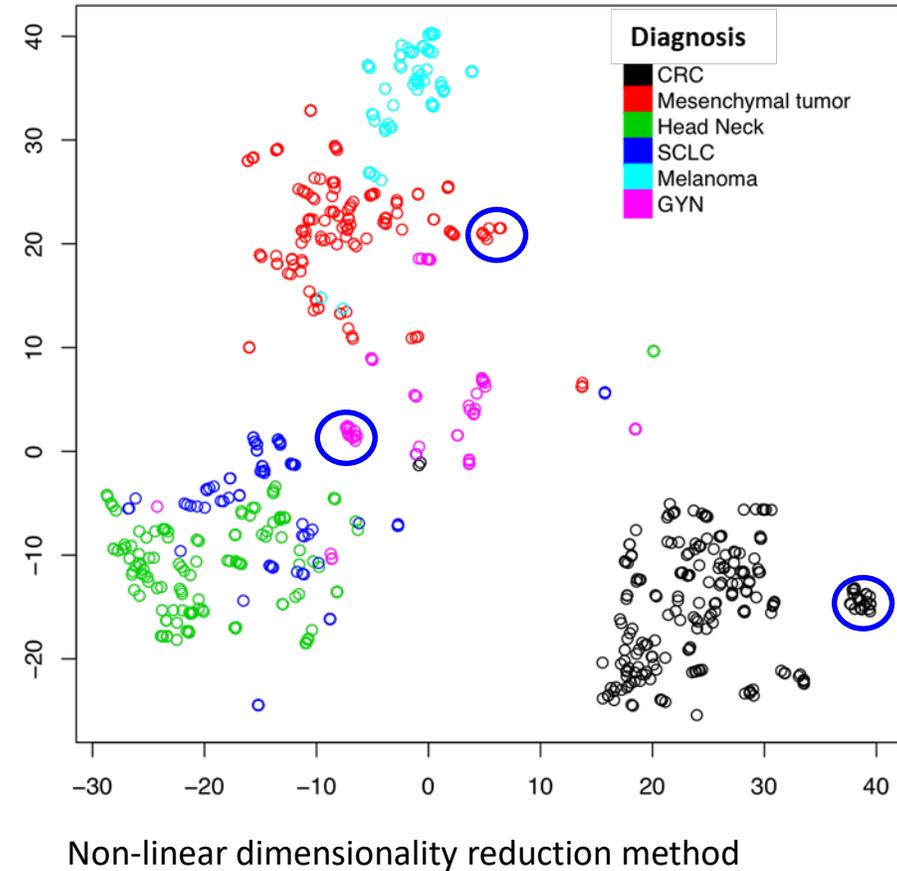
P0: Well differentiated keratinized squamous cell carcinoma, with area of keratin pearl formation.

Model Transcriptome Concordance

Hierarchical Clustering of PDX Models Across Passages
> Pairwise Spearman Correlation



Individual PDXs Cluster by Model and Disease Type
> t-SNE Analysis of RNASeq



Sampling includes RNASeq profiles from Patient material (Originator) and representative PDXs from Passage 0-3

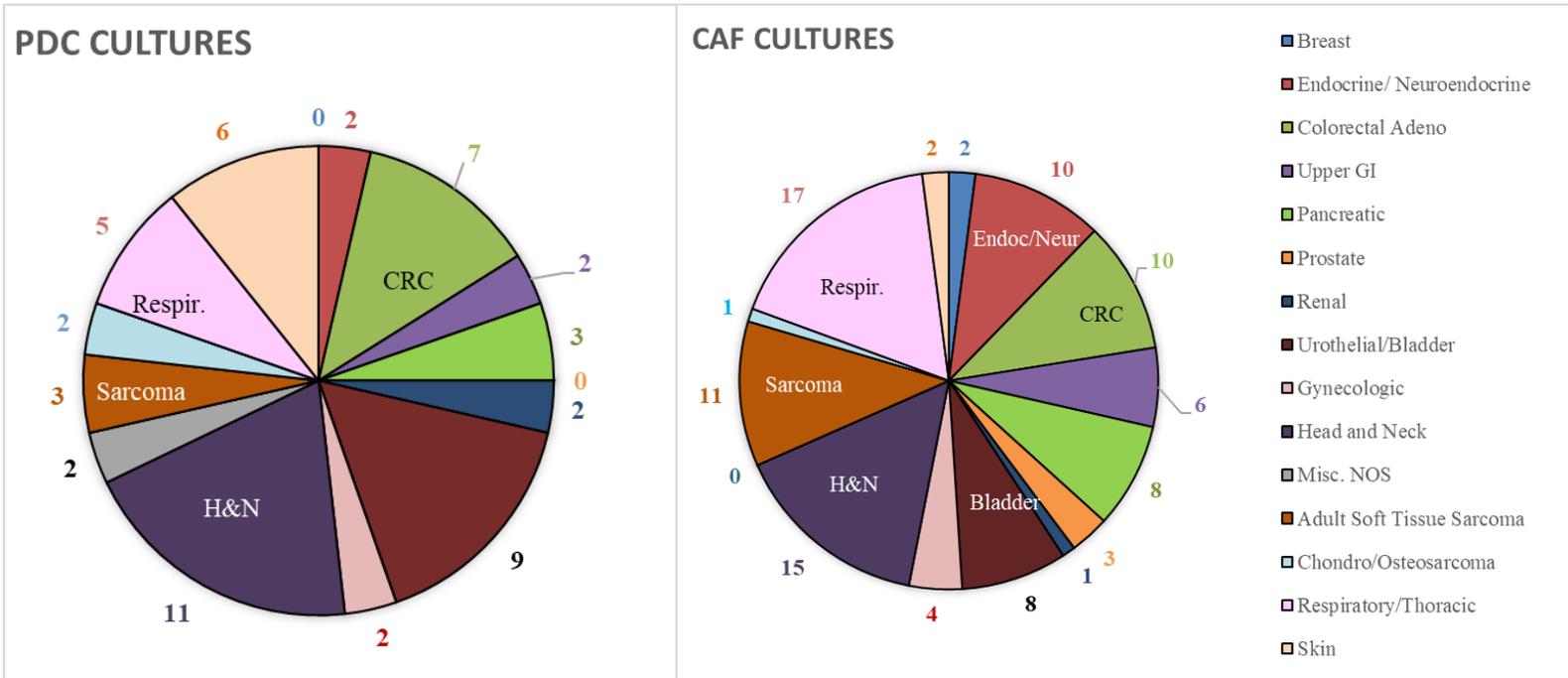
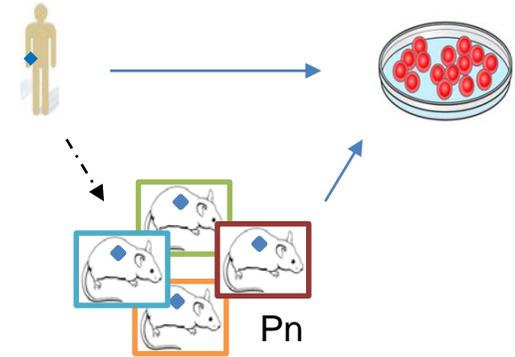
Release of In Vitro Early-Passage Patient-Derived Tumor Cultures (PDC) and Cancer-Associated Fibroblasts (CAF)

June/July 2018

Finalizing database logic and website content for public release

Will be announced on DCTD website and @NCItreatment Twitter account

- Expect 50-70 PDC [Median passage 20] and >100 CAF [Median passage 15] at launch
- At least 1/3 currently matched to a Public PDX (more in development)
- 6 Matched PDC/CAF cultures (more in development)

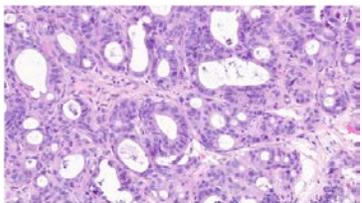
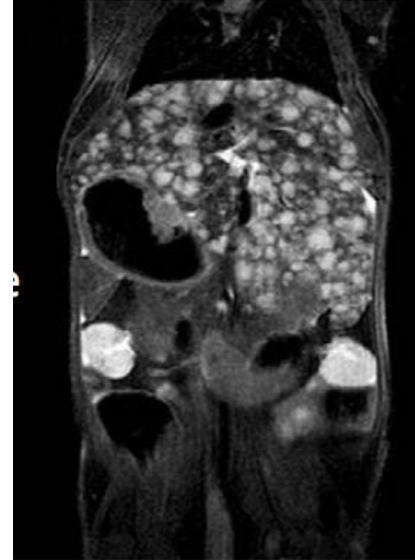


- SOPs to be provided on Public website
- All PDCs tested for growth as a xenograft
- All PDCs will have WES and RNASeq available
- CAFs are not transformed. They will have limited number of passages before senescence.

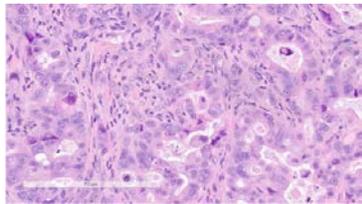
PDMR In Development



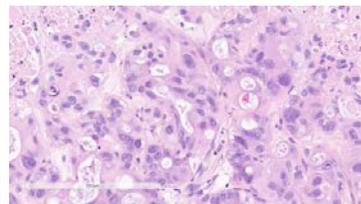
- **Germline Sequence for sub-set of models**
- Consensus Genomic Variants: List of variants that are 100% represented in WES data
- Designation of Metastatic PDX Models (spontaneous, post-debulking)
- Whole Mouse Imaging (e.g., MRI, US, CT) via TCIA
- Preclinical Drug Study Results
- Models Developed from Rapid Autopsy Procedures:
 - Current focus is on Pancreatic and Prostate Cancer
 - PDX Models from Primary and Metastatic Locations in the Same Patient



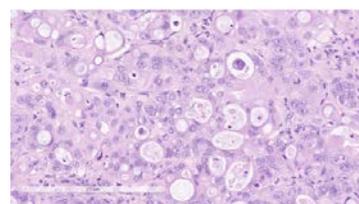
1°: Pancreas



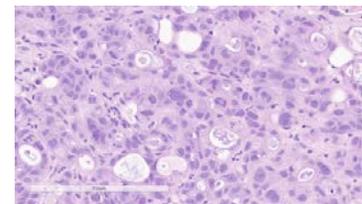
Met: Liver



Met: Colonic Fat



Met: Myometrium



Met: Colon

NCI Patient-Derived Models Repository (PDMR) Posters

April 16: 8AM – 12PM

Session PO.TB01.01 - Advances in the Generation and Analysis of Patient-Derived Xenografts

1038 / 11: Xenograft-associated B cell lymphoproliferative disease as a surrogate model to study Epstein-Barr virus (EBV) driven lymphoma of the elderly

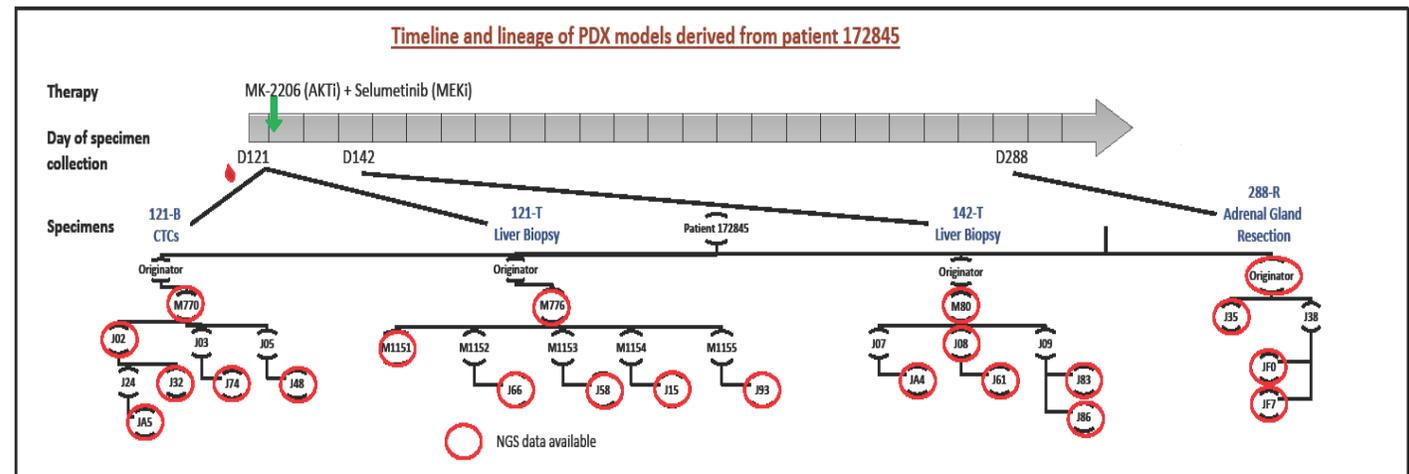
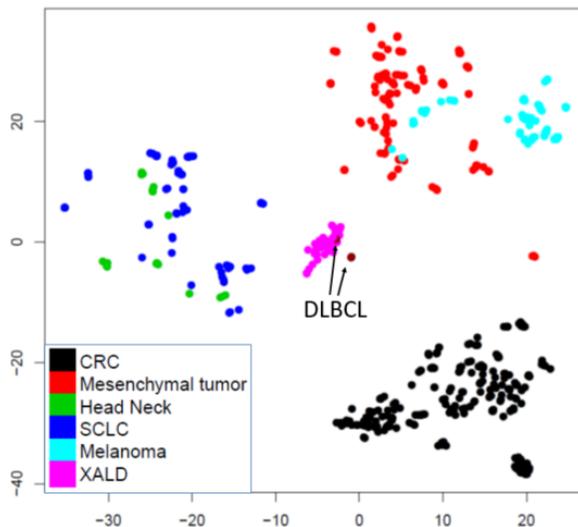
Tomas Vilimas et al.

1039 / 12: PDX models generated from a patient with metastatic colon adenocarcinoma display both spatial and temporal tumor heterogeneity

Biswajit Das et al.

XABLD cases cluster with ABC-subtype DLBCL

► t-SNE plot: RNA-seq data of XABLD cases (n=26)



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In vivo & In vitro Teams

Dianne Newton
Kaitlyn Arthur
Mariah Baldwin
Carrie Bonomi
Suzanne Borgel
Devynn Breen
John Carter
Tiffanie Chase
Margaret R. DeFreitas
Jordyn Davidson
Emily Delaney
Raymond Divelbiss
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Kyle Georgius
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Kelly Hedger
Sierra Hoffman

Candace Mallow
Chelsea McGlynn
Malorie Morris
Jenna E. Moyer
Michael Mullendore
Kevin Plater
Marianne Radzyninski
Nicki Scott
Luke H. Stockwin
Howard Stotler
Jesse Stottlemeyer
Savanna Styers
Debbie Trail
Anna Wade
Abigail Walke
Jordan Welker

Molecular Characterization

Laboratory (MoCha)

P. Mickey Williams
Chris Karlovich
Corrinne Camalier
Erin Cantu
Lily Chen
Biswajit Das
Vivekananda Datta
Palmer Fliss
Thomas Forbes
Wiem Lassoud
Jason Lih (Pharmacoclytics)
Sean McDermott
Rajesh Patidar
Tomas Vilimas
Bill Walsh

Whole Mouse Imaging

Paula Jacobs
James Tatum
Joseph Kalen
Lilia Ileva
Nimit Patel
Lisa Riffle

Statistics

Larry Rubinstein
Eric Polley (Mayo)
Mariam Konate

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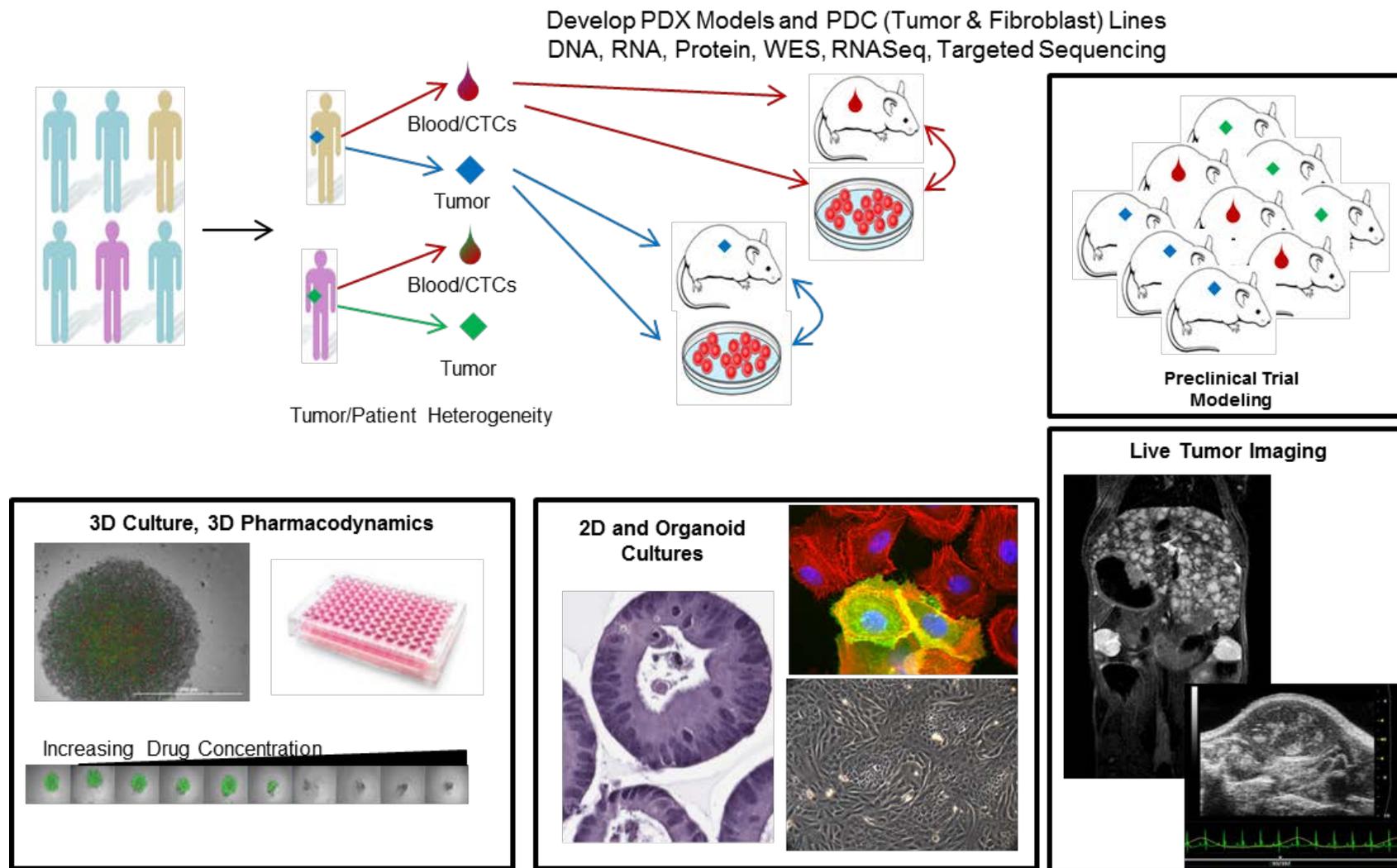
PDMR NCI Patient-Derived Models Repository
An NCI Precision Oncology InitiativeSM Resource

pdmr.cancer.gov



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NCI Patient-Derived Models Repository: Multiple Avenues for Discovery



Genetic Ancestry Assessment for 255 PDX Models with WES

